IV. REMARKS ON THE AMENDMENT TO THE CLAIMS

- Claims 1-8 were canceled, without prejudice, to eliminate certain issues in the event of an appeal. Applicants maintain the right to file a divisional or continuation application to the canceled claims.
- Claim 46 was amended to remove the preamble, which is ordinarily given no patentable weight by The Office. Other changes were made to incorporate the elements of the preamble into the claim body as well as to clarify the claim language.
- Claim 47 was amended to remove "the step of" from the preamble, which is ordinarily given no patentable weight by The Office.
- Claim 48 was amended to remove "the step of" from the preamble, which is ordinarily given no patentable weight by The Office.
- Claim 83 was amended to remove the preamble, which is ordinarily given no patentable weight by The Office. Other changes were made to incorporate the elements of the preamble into the claim body as well as to clarify the claim language.
- Newly added claims 88-98 are based in substantial part on claims 50-59 as originally filed. Claims 92 and 93 are based upon claim 54 as originally filed. Antecedent basis for these claims can be found throughout the specification, but in particular can be found in claims 50-59, as originally filed, as well as at page 22, line 10 to page 23, line 28 of the specification.
- Newly added claims 99-104 are based in substantial part on claims 35, 36, 38, 39, 42 and 45 as originally filed. Antecedent basis for these claims can be found throughout the specification, but in particular can be found in claims 35, 36, 38, 39, 42 and 45, as originally filed, as well as at page 17, line 19 to page 19, line 30 of the specification.

Because the filing receipt acknowledges that Applicants paid for 48 total claims and 8 independent claims, it is believe that this amendment can be entered without the payment of an additional fee. As amended, there are 46 total claims and 7 independent claims, one of which (Claim 34) has been withdrawn by the Examiner.

Although it is acknowledged that newly added claims 99-104 depend from a claim withdrawn by the Examiner, it is believed that entry of this amendment is a matter of right given the non-Final nature of the present Office Action. Further, Applicants are petitioning for withdrawal of the Restriction Requirement that resulted in withdrawal of claim 34. In the event that Applicants are successful in their petition, newly added claims 99-104 should properly be examined. If Applicants petition is not successful, these new claims can be canceled.

It is believed that no new matter has been added to the application by this amendment.

V. RESPONSE TO REJECTIONS UNDER 35 U.S.C. § 103(a)

(i) The Law

"A claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter as a whole (emphasis added) would have been obvious at the time the invention was made to a person of ordinary skill in the art." *In re Dembiczak*, 175 F.3d 994, 998, 50 U.S.P.Q.2d 1614, 1616 (Fed. Cir. 1999). In determining whether a claimed invention is obvious one must consider; 1) the scope and content of the prior art; 2) the level of skill in the prior art; 3) the differences between the claimed invention and the prior art; and 4) objective evidence of non-obviousness such as secondary factors. *Id.*

The PTO bears the burden under 35 USC § 103 to establish an unrebutted *prima facia* case of obviousness. *In re Rouffet*, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453, ___ (Fed. Cir. 1998). To satisfy its burden, the PTO must show some objective teaching in the prior art or that knowledge generally available in the art would lead the ordinary practitioner to combine relevant teaching. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). In the absence of a proper *prima facia* case of obviousness, an Applicant is entitled to a patent. *In re Rouffet*, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453, ___ (Fed. Cir. 1998). To overcome a claimed *prima facia* case of obviousness, an Applicant can either show that the *prima facia* case of obviousness is insufficient because it relies on incorrect factual predicates or otherwise present secondary evidence of non-obviousness. *Id.*

A proper rejection under 35 USC § 103 may not be premised upon "bald assertions" for which there is no support for or explanation of a conclusion. *Id.* An Examiner's cursory statement unaccompanied by evidence or reasoning is entirely inadequate to support a rejection. *In re Sichert*, 566 F.2d 1154, 1164, 196 U.S.P.Q. 209, 217 (C.C.P.A., 1977). A rejection based on section 103 must be based in fact that is not aided by hindsight. *In re Warner*, 54 C.C.P.A. 1628, 1635, 379 F.2d 1011, 1017, 154 U.S.P.Q. 173, 178 (C.C.P.A., 1967). The PTO may not resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in its factual basis for a rejection. *Id.* Doubts as the factual basis for a rejection must to resolved in favor of the Applicant since it is the PTO's burden to establish a *prima facia* case of obviousness. *Id.*

(ii) The Facts

- The Examiner has acknowledged that Kosse does not teach enzyme-linked probes for the analysis of yeast, particularly *Dekkera bruxellensis* (OA at page 5).
- The Examiner has specifically stated that Kosse: "... teaches that prior to *in situ* hybridization, yeast cell walls **must be permeablized** (emphasis added) and that probes **must be selected to yeast 18 rRNA which are fully accessible to probes** (emphasis added) (see page 478)." (OA at page 4).
- Kosse specifically describes the importance of permeablization of the cell wall of yeast else probes will not penetrate and the yeast cannot be determined (Kosse at page 474, col. 1, first full paragraph). Kosse specifically describes treatment of the yeast cells with **lyticase** to permeablize the cells to the flourescently labeled probes. *Id.*
- Kosse specifically teaches that only the 3' end of the 18S rRNA is accessible to fluorescently labeled probes and that the other variable regions of 18S rRNA were not accessible to *in-situ* hybridization. (Abstract and page 478, col. 2, first full paragraph).
- Stender (1998) does not teach anything about yeasts but is limited to determinations of mycobacteria.
- Stender (1998) teaches enzyme-linked probes for the determination of mycobacteria but does not teach about permiabilizing yeast cells to enzyme-linked probes.
- Stender (1998) did not actually use enzyme-linked probes in any assay and does not appear to have appreciated the difficulty that Amann et al. specifically describes with regard to getting large probes (e.g. enzyme-linked probes) into cells having a cell wall.
- Amann et al. (Reference CA) specifically teach that enzyme-linked probes **WOULD NOT** penetrate into yeast cells (Abstract and pages 3008-3010, section entitled "Penetration of HRP-labeled oligonucleotides into whole fixed cells). Amann et al. specifically explain that with a horseradish peroxidase label, the oligonucleotide probe is approximately 100 time

larger than is a fluorescently labeled probe (Amman et al. at page 3008, bottom of col. 2). Amann et al. also teach that cells of *Saccharomyces cerevisiae* (a yeast) were not determinable with enzyme-linked probes even when treated with enzymes (**lyticase** and β-glucoronidase) or detergents (Amann at page 3010, middle, col. 1). It is noted that **lyticase** is the same enzyme that Kosse used to permeablize yeast to fluorescently labeled oligonucleotide probes and Amann et al. specifically teach that said **lyticase** enzyme does not work to permeablize *Saccharomyces cerevisiae* to enzyme-linked oligonucleotide probes. Stender (1998), discussed above, is silent to this particular issue.

(iii) Rebuttal To The Rejection Based Upon Kosse And Stender (1998)

At paragraph 2 of the present Office Action, the Examiner has rejected claims 1-8 and 46 under 35 U.S.C. §103(a) as being unpatentable over Kosse in view of Stender (1998). Claims 1-8 have been canceled and therefore the rejection as to these claims has been rendered moot. Applicants respectfully traverse this rejection as to claim 46.

As previously stated, it behooves The Office to properly state the basis for rejecting claimed subject matter else the Applicant is entitled to the grant of his letters patent. It is further submitted that a proper rejection under 35 U.S.C. §103(a) must recite not only where each of the elements/limitations of the claimed subject matter are found in two or more references but The Office must also establish a clear **motivation**, based upon the teachings of the references, to combine the references in the manner presently claimed. It is respectfully submitted that the rejection articulated at paragraph 3 of the present Office Action does not state any **specific motivation** to combine the references and is therefore *prima facia* deficient. Moreover, it is believed that the statement of the rejection is hindsight based and self-fulfilling. Accordingly, it is respectfully submitted that the stated rejection of claims 1-8 and 46 over Kosse in view of Stender (1998) should properly be withdrawn.

Furthermore, there can be no motivation to combine Kosse and Stender (1998) because Kosse teaches only about yeasts and Stender (1998) teaches only about mycobacteria. Kosse implicitly teaches away because they did not use enzyme-linked probes (Examiner's admission noted above) and they expressly stated that the cell walls

must be permeablized to the probes (see the Facts summarized above). Although Stender (1998) teaches enzyme-linked probes, such probes are used only to analyze mycobacteria (not yeast) and therefore Stender (1998) does not teach about permeablizing yeast cells to enzyme-linked probes. It seems that, at the time of the invention, the problem of permeablizing yeast cells to enzyme-linked probes had been addressed only by Amann et al. and they failed (see the Facts summarized above). Accordingly, it is clear that no motivation could possibly exist for combining Kosse with Stender to thereby achieve enzyme-linked probes for the *in-situ* analysis of yeasts, such as *Dekkera/Brettanomyces*, since it was well established that the yeast cell wall could not be easily permeablized to large molecules such as enzymes. Moreover, the only known attempts at attempting to penetrate the cell wall of yeast with an enzyme-linked probe had failed. These facts are clear based upon the express teachings of the references.

In addition to the foregoing, it is respectfully submitted that the ordinary practitioner is without a reasonable expectation of successfully applying an enzyme-linked probe for the *in-situ* determination of yeast. Amann et al. (Reference CA) is the most specific teaching on this subject matter and it **clearly teaches away** from the presently claimed subject matter since they tried and failed. This fact is clear based upon the express teachings of the references.

Moreover, it is respectfully reiterated from past responses that the present rejection can best be characterized as being a hindsight based synopsis of that which might be "obvious to try" where the art does not provide any express teachings as to how to achieve the claimed invention, but more importantly, provides at least one example of failure. It is respectfully submitted that the failure by Amann et al. to achieve success with an embodiment of the present invention speaks volumes about the patentability (i.e. non-obviousness) of the present invention.

Comments on the Examiner's Rebuttal Arguments:

At the outset of the rebuttal, the Examiner suggests that "The motivation for combining the teachings of various references need not be explicitly found in the references themselves, but may be provided by the examiner based on logic and sound scientific reasoning (OA at page 7). Although this may be a fair statement of the law, the reasoning must be based upon fact and not on supposition or bald assertions.

What a reference teaches is a question of fact. *In re Bell*, 991 F.2d 781, 784, 26 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1993). Amann et al. expressly makes the following specific statements.

"Hitherto we had not achieved penetration of enzyme-labeled probe into gram positive bacteria or **yeast cells** (emphasis added)." Amann et al., Abstract, page 3007.

"However, since the high-molecular weight enzyme-antibody conjugate must penetrate the cell wall of the fixed target cells, this approach has not served to visualize any gram-positive bacteria so far examined." Amann et al. at page 3007, col. 2, lines 3-7.

"The molecular weight of horseradish peroxidase (40,000) is approximately 100 times greater than that of the fluorsecein or tetramethylrhodamine, the two most common labels of rRNA-targeted oligonucleotide probes for single-cell identification. This increases the overall molecular weight of the probe from about 6,000 to about 50,000, and penetration of enzyme-linked probe through the cell periphery might be expected to hinder whole-cell identification." Amann et al. at page 3008, col. 2, lines 51-59.

"On the other hand, the gram-positive bacteria examined (B. subtilis and several strains of lactococci) remained **impermeable to the HRP-labeled probe** even after prolonged incubation with lysozyme, lysostaphin (Sigma), or mutanolysin (Sigma) at different concentrations. Following extensive digestion, the gram-positive bacteria were only partly stained while gram positive bacteria, added as a control, were lysed (data not shown)." Amann et al. at page 3010, col. 1, lines 5-13.

"In an attempt to increase hybridization of the fixed gram positive cells, we included the detergents EDT20, SDS, Triton X-100, Tween 20, and Cetrimide (all from Sigma) at various concentrations. With the exception of Triton X-100, there detergents had no influence on the hybridization. Inclusion of 1% Triton X-100 in the hybridization buffer resulted in intracellular substrate precipitation within fixed cells of B. subtilis and Lactococcus lactis (harvested during exponential growth), using probe Eub338. **Since even in an actively growing pure culture only some cells were stained, enzyme-labeled oligonucleotides cannot be currently used for specific single-cell identification of gram positive bacteria** (emphasis added). We encountered similar problems with cells of Saccharomyces cerevisiae, and again attempts to make the intracellular RNA accessible by enzymatic treatment (lyticase and β-glucoronidase; both

from Sigma) of the cells or detergent addition **failed** (emphasis added)." Amann et al. at page 3010, col. 1, lines 28-35.

Taken as a whole, logic and sound scientific reasoning dictates only one conclusion from Amann et al. They tried and failed to apply enzyme-linked probes to the *in-situ* hybridization analysis of yeast. Try as the Examiner may, this fact is inescapable. Based upon the record, it seems that nobody else has ever attempted to perform an *in-situ* hybridization assay on yeast using an enzyme-linked probe – likely because Amann et al. reported that they tried and failed as well as gave a detailed explanation as to why large molecules (such as enzyme-linked probes) have difficulty penetrating the cell.

To the extent that the Examiner believes that the teachings of Amann et al. have been mischaracterized by Applicants, this is simply not true. Moreover, it is respectfully submitted that it is the Examiner who mischaracterizes the art by ignoring the fact that Amann et al. expressly describe attempting to perform an *in-situ* based assay with an enzyme linked probe on a yeast and they admitted that they failed. Based upon these teachings it is simply implausible for the Examiner to assert that the teachings of Amann et al., Kosse and Stender (1998) in combination with knowledge in the art would provide the ordinary practitioner with enablement, motivation and a reasonable expectation of success (OA at page 7-8 bridging paragraph) in performing any *in-situ* assay of yeast using an enzyme-linked probe. It is respectfully submitted that this is illogical, self-serving supposition and not sound scientific reasoning.

In various arguments, the Examiner asserts that the specification and/or claims provide no teachings as to the critical steps that must be performed in order to allow for the detection of yeasts by *in-situ* hybridization. The short rebuttal to this assertion is: "so what?". The question to be answered in view of the present rejection is whether or not the ordinary practitioner, having knowledge of Kosse and Stender (the two references combined to form an asserted "*prima facia*" case for obviousness), would be enabled, motivated and possess a reasonable expectation of successfully performing an *in-situ* hybridization assay on a yeast using an enzyme-linked probe. That Amann et al. failed, leads to the obvious answer – NO. Why Amann et al. failed is unknown and irrelevant. Since the art, considered as a whole, weights against the asserted *prima facia*

case for obviousness, Applicant is entitled to a granting of the patent. *In re Rouffet*, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453, ___ (Fed. Cir. 1998).

In support of maintaining the present rejection, the Stender Declaration under 37 C.F.R. § 1.132 was summarily dismissed as "a statement of opinion by one of the present inventors ...." (OA at page 10). Applicants must respectfully disagree with this assessment.

The Declaration of Dr. Stender is sworn under penalty of perjury and therefore should not be cursorily dismissed. Moreover, in addition to being a well-established scientist in the relevant field for 11 years and a co-inventor in the present application, Dr. Stender is a co-inventor of the invention described in the Stender (1998) reference that has been cited against the present application. Accordingly, Dr. Stender's opinions, insights and analysis are quite relevant to accessing the validity of the present rejection under 35 U.S.C. § 103(a). According to his Declaration, said opinions are formulated based upon his knowledge of the art as well as his review of the references. It is apparent that Dr. Stender's stated opinions disagreed with the Examiner's assertions and this may explain why they were not properly considered. Regarding the assertion that Dr. Stender's comments do not address the teachings of the art as a whole, it can only be stated that as a practitioner of 11 years having read all of the specific references now being discussed, it is unclear how the Examiner could reasonable reach such a conclusion.

Near the end of the rebuttal argument, a newly cited Amann et al. (Microbiological Reviews, March 1995 59(1): 143-169) reference was discussed in combination with the previously discussed Amann et al. reference (Reference CA). Simply put, Amann et al. (Microbiological Reviews, March 1995 59(1): 143-169) does not contradict anything said in Reference CA and specifically does not state that it is possible to apply enzyme-linked probes to the *in-situ* analysis of yeasts. Accordingly, this new reference does not add anything to the Examiner's case. In fact, it weakens her argument since apparently after three additional years of work, Dr. Amann still was not been able to perform an *in-situ* assay on yeast using an enzyme-linked probe else he most certainly would have so reported in this later publication. That he did not is highly relevant to the Examiner's assertions that conclusory statement of Reference CA supports the obviousness argument (OA at page 20).

In view of the foregoing remarks, as well as the amendment set forth herein, it is respectfully submitted that the present rejection of claims under 35 U.S.C. §103(a) over Kosse in view of Stender (1998) should be withdrawn. Reconsideration is requested.

(iv) Rejection based upon Kosse in view of Stender (1998) and Parton (5,905,038)

At paragraph 3 of the present Office Action, the Examiner has rejected claims 47-49 and 80-85 under 35 U.S.C. §103(a) as being unpatentable over Kosse in view of Stender (1998) and further in view of Parton (US 5,905,038). Applicants respectfully traverse this rejection.

This rejection is cumulative with the rejection articulated in paragraph 2 of the Office Action. Accordingly, for the reasons described above, it is believed that this rejection cannot properly stand as being dependent upon an improper combination of Kosse and Stender (1998).

Applicants note in particular that claims 46 and 83 require the detection of enzyme activity within the yeast. Accordingly, it cannot be reasonably asserted that these claims do not apply to a method whereby the enzyme-linked probe must penetrate into the yeast. Since claims 47-49 are dependent upon claim 46 and claims 84-85 dependent on claim 83, these claims likewise pertain to a method whereby the enzyme-linked probe must penetrate into the yeast.

In addition to the foregoing, Applicants add that the rejection articulated at paragraph 3 of the present Office Action does not state any specific motivation to combine the references and is therefore *prima facia* deficient. Moreover, it is believed that the statement of the rejection is hindsight based and self-fulfilling.

In view of the foregoing remarks, as well as the amendment set forth herein, it is respectfully submitted that the present rejection of claims under 35 U.S.C. §103(a) over Kosse in view of Stender (1998) and in further view of Parton should be withdrawn. Reconsideration is requested.

(v) Rejection based upon De Wachter in view of Kosse and Stender (1998)

At paragraph 4 of the present Office Action, the Examiner has rejected claims 1-8, 10-12, 16, 18-19, 21-26, 29, 32, 46, 61-62, 86 and 87 under 35 U.S.C. §103(a) as being

unpatentable over De Wachter in view of Kosse and in further view of Stender (1998). Applicants respectfully traverse this rejection.

This rejection is cumulative with the rejection articulated in paragraph 2 of the present Office Action. Accordingly, for the reasons described above, it is believed that this rejection cannot properly stand as being dependent upon an improper combination of Kosse and Stender (1998).

Furthermore, in formulating this rejection, the Examiner has argued: "De Wachter teaches an isolated nucleic acid consisting of the sequence of 18S rRNA of *Dekkera/Brettanomyces bruxellensis*. The 18S rRNA of De Wachter comprises the sequence of SEQ ID NO: 1 (see nucleotides 1066-1052 of GenBank Accession No. X58052). The nucleic acid of De Wachter **is considered to have the property** of being suitable as a probe for the detection, identification or quantitation of *Dekkera/Brettanomyces bruxellensis*.(emphasis added)" (OA at page 15) From this final statement, it is clear that the Examiner has taken the conclusory position that the entire sequence disclosed by De Wachter can be used as a basis to construct probes for the determination of *Dekkera/Brettanomyces bruxellensis*. Accordingly, the Examiner's argument is completely undermined where statements in the art relied upon by the Examiner to reject Applicant's claims challenges this conclusory position.

More specifically, Kosse specifically teaches that only the 3' end of the 18S rRNA is accessible to fluorescently labeled probes and that the other variable regions of 18S rRNA were not accessible to *in-situ* hybridization. (Abstract and page 478, col. 2, first full paragraph). Moreover, the Examiner has previously **admitted** that Kosse: "... teaches that prior to *in situ* hybridization, yeast cell walls **must be permeablized** (emphasis added) and that probes **must be selected to yeast 18 rRNA which are fully accessible to probes** (emphasis added) (see page 478)." (OA at page 3) Consequently, it is not reasonable for the Examiner to baldly assert that any nucleobase sequence that is homologous to the gene sequence described by De Wachter will be useful to produce an *in-situ* hybridization probe.

In her rebuttal to this argument, the Examiner states: "All probes disclosed by Kosse were found to be useful for dot blot hybridization, regardless of whether they were derived from the 5' end or the 3' end" (OA at page 19). If the Examiner's interpretation of Kosse is correct, then why did Kosse expressly state:

> *"18S rRNA-targeted oligonucleotide probes were designed for rapid and reliable identification of yeasts involving spoilage of dairy products. ... Whole cell hybridization experiments revealed that the 3' end of the target molecule is a suitable site for fluorescently labeled species specific nucleic acid probes which detect S. cerevisiae, P. anomala, D. hansenii and D. bruxellensis in situ. Other variable regions of the 18S rRNA tested for species specific probes were not accessible to in situ hybridization" (Kosse Abstract).*

and:

> *"Experiments with a variety of species-specific fluorescently labeled oligonucleotides revealed that only the 3'-end of 18S rRNA is accessible for species specific probes.* ***Unexpectedly*** *(emphasis added), only the probes Dha 1708 for D. hansenii, Dbr 1700 for D. bruxellensis, Pan 1710 for P. anomala and Sce1711 for S. cerevisiae yielded strong fluorescent signals (Fig 4A, B)." (Kosse at page 474, col. 1).*

The contradiction between the Examiner's assertions and the actual teachings of Kosse is self-evident. That the Examiner has relied upon a misinterpretation of the teachings of a reference in formulating the present rejection can lead to only one logical conclusion. The rejection is based upon incorrect factual predicates and therefore is improper. *In re Rouffet*, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453, ___ (Fed. Cir. 1998). For this reason alone the rejection should be withdrawn.

In addition to the foregoing, it is respectfully submitted that the rejection articulated at paragraph 4 of the present Office Action does not state any specific motivation to combine the references and is therefore *prima facia* deficient. Moreover, it is believed that the statement of the rejection is hindsight based and self-fulfilling.

In view of the foregoing remarks, as well as the amendment set forth herein, it is respectfully submitted that the present rejection of claims under 35 U.S.C. §103(a) over De Wachter in view of Kosse and Stender (1998) should be withdrawn. Reconsideration is requested.

(vi) Rejection based upon De Wachter in view of Kosse and Stender (1998) and further in view of Parton

At paragraph 5 of the present Office Action, the Examiner has rejected claims 47-49 and 80-85 under 35 U.S.C. §103(a) as being unpatentable over De Wachter in view of

Kosse and Stender (1998) in further view of Parton (US 5,905,038). Applicants respectfully traverse this rejection.

This rejection is cumulative with the rejection articulated in paragraphs 2, 3 and 4 of the present Office Action. Accordingly, for the reasons described above, it is believed that this rejection cannot properly stand as being dependent upon an improper combination of Kosse and Stender (1998), with or without the combination of De Wachter.

In addition to the foregoing, it is respectfully submitted that the rejection articulated at paragraph 5 of the present Office Action does not state any specific motivation to combine the references and is therefore *prima facia* deficient. Moreover, it is believed that the statement of the rejection is hindsight based and self-fulfilling.

In view of the foregoing remarks, as well as the amendment set forth herein, it is respectfully submitted that the present rejection of claims under 35 U.S.C. §103(a) over De Wachter in view of Kosse, Stender (1998) and Parton should be withdrawn. Reconsideration is requested.

VI. SUMMARY

It is believed that this response addresses all rejections set forth in the present Office Action and the application is in ready condition for allowance. In consideration of the preceding amendments and remarks, Applicants hereby respectfully request reconsideration of all pending claims (as amended herein), the withdrawal of all rejections set forth in the present Office Action and issue of a Notice of Allowance by The Office.

VII. INTERVIEW

If the Examiner believes a telephonic or personal interview would advance the prosecution of the subject application, the Examiner is invited to contact attorney Gildea during business hours at the telephone or facsimile numbers listed below.

VIII. FEES

Except for the fee due for consideration of the petition under 37 C.F.R. §1.136(a) and the fee due for consideration of the petition under 37 C.F.R. § 1.144 or 1.181, it is

believed that no additional fees are believed due The Office for consideration of this paper. Applicants note that the amendment set forth herein adds several additional claims. However, the record reflects that Applicants have paid for 48 total claims and 8 independent claims. Since the claim count after entry of the present amendment is 46 total claims and 8 independent claims, it is believed that no additional fee is due for consideration of the claims as amended. If however, The Office determines that any other fee is due, authorization is hereby granted to charge any required fee associated with the filing and consideration of this paper to Deposit Account 01-2213 (Order No: BP9901-US).

IX. CORRESPONDENCE/CUSTOMER NUMBER

Please send all correspondence pertaining to this document to:

Brian D. Gildea, Esq.
Applied Biosystems
500 Old Connecticut Path
Framingham, MA 01701

Telephone: 508-383-7632
Fax: 508-383-7468

IF NOT ALREADY DONE, PLEASE MATCH THIS CASE WITH CUSTOMER NUMBER

23544

Respectfully submitted
on behalf of Applicants,

July 22, 2005

Brian D. Gildea, Esq.; Reg. No. 39,995